Interim statement on the use of additional booster doses of Emergency Use Listed mRNA vaccines against COVID-19

The World Health Organization, with the support of the Strategic Advisory Group of Experts (SAGE) on Immunization and its COVID-19 Vaccines Working Group, continues to review the emerging evidence on the need for and timing of additional booster doses for the currently available COVID-19 vaccines which have received Emergency Use Listing (EUL). The statements and conclusions in this document will be updated as new data become available.

The objective of this statement is to review the evidence on additional booster doses. In considering additional booster doses, there are two main scenarios to assess: 1) the use of additional booster doses in those who are not able to mount and sustain adequate immune responses and 2) considerations for additional booster doses to be administered in order to protect high risk populations and health workers in order to maintain the health system during periodic waves of disease surges.

WHO`s current Recommendations: (1) initial booster doses:

Booster doses should be offered based on evidence that doing so would have substantial impact on reducing hospitalization, severe disease and death, and to protect health systems. The order of implementing booster doses to different population groups should follow that which has been laid out for the primary vaccination series – i.e., booster doses should be prioritized for higher priority-use groups before lower priority-use groups, unless there is adequate justification not to do so. Such justification may include programmatic constraints or acceptability obstacles to uptake in higher priority-use groups that would result in vaccine wastage. In such cases, strategies should be prioritized to improve vaccine delivery, community engagement, and social mobilization efforts to reach higher priority-use groups.

Within a given priority-use group, primary series vaccination will have greater impact per dose than additional doses. Across priority-use groups, the benefits of additional doses for higher priority-use groups versus primary series doses for lower priority-use groups depends on country conditions, including supply and roll-out timelines, past epidemic dynamics and infection-induced immunity, vaccine product, vaccine effectiveness, and waning of protection. When high primary series coverage rates have been achieved among subgroups at higher risk of severe disease and death (e.g., older adults), additional doses for these subgroups may yield greater reductions in severe disease and death than use of equivalent vaccine supply for primary series vaccination of lower priority-use groups.

The optimal interval between completion of a primary series and administration of additional doses has yet to be determined, and depends on epidemiological setting, vaccine product, targeted age groups, background seroprevalence, and circulation and frequency of specific variant of concerns (VoC). As a general principle, an interval of 4–6 months since completion of the primary series could be considered, especially in the context of Omicron.

Booster doses should be considered for all COVID-19 vaccines having received EUL as per WHO's product specific interim recommendations.

WHO`s current Recommendations: (2) Additional Doses in Immunocompromised persons

Available data for WHO EUL COVID-19 vaccine products suggest that vaccine effectiveness and immunogenicity are lower in immunocompromised persons (ICPs), compared to persons without immunocompromising conditions. An additional dose included in an extended primary series enhances immune responses in some ICPs (2, 3). Given the significant risk of severe COVID-19 for ICPs, if infected, WHO has already issued a recommendation for an extended primary series (i.e. third dose) as

well as a booster dose (i.e. fourth dose) for ICPs, for all COVID-19 vaccines (1, 4). Homologous (same vaccine platform) and heterologous (different vaccine platform) vaccines can be used for such booster doses (5).

Considerations for additional booster doses beyond the first booster (< 6 months since first booster)

Additional booster doses beyond the first booster dose are currently being offered by some countries (i.e. fourth dose to older adults and a fifth dose for immunocompromised persons). Data on the usefulness of these additional booster doses is sparse and especially limited on the duration of further protection. Data on additional booster doses as of May 2022 only exists for the mRNA vaccines, and not for other vaccine platforms. Hence, in the following we only focus on the evidence with regards to additional booster for mRNA vaccines, while encouraging more data to be accrued for all vaccine platforms.

Seven studies were available for review, six of which were from Israel (6-11) and one from Canada (12). All were conducted during a time when Omicron has been the predominant circulating strain globally. While the studies vary in their design and population investigated, most evaluated the relative effectiveness of a fourth dose 4 months after a 3rd dose of mRNA vaccine compared to those who received 3 doses. This relative vaccine effectiveness only provides evidence on the value of a fourth dose compared to individuals who already have some vaccine induced protection (3 dose recipients). The relative vaccine effectiveness depends upon the initial VE provided by 3 doses and how much subsequent waning has occurred. In contrast, earlier studies provide an absolute vaccine effectiveness comparing vaccinated versus unvaccinated individuals. The Canadian study is the only available study that provides data on absolute vaccine effectiveness (i.e., compares 4th dose schedule to those who are unvaccinated). Additionally, the maximum follow up in the available studies was short and ranged from two weeks to ten weeks after the fourth dose.

Of the seven studies that investigated the use of a 4th dose of mRNA COVID vaccine, two reported specifically on outcomes of infection and any symptomatic disease (10, 11). Both studies were conducted in Israel and included health workers (HWs) as their population of interest. One study showed an increased IgG antibodies against SARS-CoV-2 receptor-binding domain and neutralizing antibody titers by a factor of 9-10 measured after fourth dose of vaccine. This corresponded to antibody titers that were slightly higher than those achieved after the third dose, with no significant difference between the two mRNA vaccines (11). The second study investigated breakthrough infections in HWs who received 3 doses of BNT162b2 vaccine and provided a comparison to those who received a fourth dose of BNT162b2. In fourth dose recipients, there was a reduction in breakthrough infection rates compared to that observed after only a 3rd dose of mRNA vaccine (10).

Of the remaining five studies, all were conducted in individuals older than 60 years of age, excluding individuals who had previous SARS-Co-2 infection and specifically evaluated mRNA vaccines. Two of the studies were retrospective cohort studies using administrative data. The first study found that the relative vaccine effectiveness against severe disease to be 66% (95% CI, 57-72) 15 to 21 days after a fourth dose and 77% (95% CI, 62-86) 36-42 days after a fourth dose (6). The second retrospective cohort study reported on death as the outcome measure and found a relative vaccine effectiveness of 78% (95% CI 72-83) 7 or more days post fourth dose. The absolute risk reduction conferred by the fourth dose was 0.07% in the study (9). The third study used a test negative design and reported on severe disease. They found a relative vaccine effectiveness of 87% (95% CI 0-98) 49-69 days post fourth booster. This study reported that severe disease was a relatively rare event, occurring among <1% of both fourth dose and third dose only recipients (8). The fourth study reviewed was a target trial (application of trial design principles from RCTs to the analysis of observational data(13)) that provided outcome data for hospitalization, severe disease and death. They found a relative vaccine effectiveness of 62% (95% CI, 50 to 74) against severe COVID-19, and 74% (95% CI, 50 to 90) against COVID-19 related death comparing 3 dose recipients to 4 dose recipients. A further analysis of the risk of severe

COVID-19 from 7 days to 30 days post fourth dose was 42.1 events per 100,000 persons, as compared with 110.8 events per 100,000 persons in the 3 dose recipient control group. This corresponds to a difference in risk of 68.8 cases per 100,000 persons (95% CI, 48.5 to 91.9)(7).

The final study, conducted in Canada, investigated not only the relative vaccine effectiveness but also the absolute vaccine effectiveness when compared to unvaccinated individuals, two dose recipients as well as three dose recipients. This study found that with each additional dose, VE increased for severe disease. Absolute VE was 82% (95%CI 75-88%) as measured more than 84 days after third dose, and 92% (95%CI 87-95%) for fourth dose recipients at greater than 7 days after the fourth dose (12).

Taken together, these studies show some short-term benefit of an additional booster dose of mRNA vaccine in health workers, those over 60 years of age or with immunocompromising conditions. Data to support an additional dose for healthy younger populations are limited; preliminary data suggest that in younger people, the benefit is minimal. Moreover, follow-up time after the additional booster dose was limited, thereby precluding conclusions about duration of protection after this dose. Therefore, there is a lack of data to guide some important questions for making policy decisions. The limited available data suggest that for highest risk groups there is a benefit that supports the administration of an additional booster dose.

Administering an additional booster dose likely comes with considerable programmatic challenges in terms of vaccine delivery in many settings. The financial and opportunity cost of such programmes must also be carefully weighed against the limited incremental benefit of an additional booster dose. In those most at risk for severe disease or death (i.e. adults above the age of 60 years, or those who are not able to mount a full immune response), the additional benefit of an additional booster dose of mRNA vaccine might be warranted.

Considerations for future additional doses:

For longer-term considerations, there are significant uncertainties related to the evolution of the virus and the characteristics of future variants. Given widespread transmission of Omicron globally, continued viral evolution with the emergence of new variants or sub lineages as is already being seen. Development of a pan-SARS-CoV-2 or pan-sarbecovirus vaccines are needed, but the timeframe for their development is uncertain (14). Meanwhile, the composition of the currently available COVID-19 vaccines may need to be updated to offer better protection against new VOCs which may be antigenically distinct (14). Current vaccines based on the index virus appear to maintain high VE against severe disease also in the context of current variants of concerns, but VE estimates against infection and symptomatic diseases are lower against Omicron. Any update to vaccine composition would aim to elicit greater breadth in the immune response against circulating and emerging variants, in addition to retaining protection against severe disease and death. The performance of any updated vaccine(s) may vary depending on the nature and magnitude of previously acquired immunity, recognizing that this immunity will be dependent upon different VOCs, different types of vaccines and their timing of administration.

While seasonality is not yet fully established for SARS-COV-2, evidence from the past two years support the notion of more substantial transmission during the winter season. Therefore, for countries with either a Northern or Southern Hemisphere winter season, plans for catch-up to improve primary series coverage and boosting for those at highest risk, campaigns should take seasonality into account. In addition, in view of the uncertainty of the characteristics of new VOC, which may emerge rapidly, there may be value in establishing vaccine induced immunity using existing vaccines (i.e. index virus) complemented by a booster dose of variant vaccine to broaden the immunological response. The Technical Advisory Group on COVID-19 Vaccine Composition will provide advice on updated vaccine composition when data is available.

To that end, in order to make sound policy decisions, data will need to be generated on the performance of current and variant-specific candidate COVID-19 vaccines, including the VE, immunogenicity and safety of an additional booster dose over time and by disease outcome and priority use groups. More research is needed on the breadth, magnitude, and durability of humoral and cell-mediated immune responses to variants. Also needed is evidence to address other gaps in the evidence regarding the need for additional booster doses, which includes the duration of VE of inactivated, subunit and viral vectored vaccines over time and by disease outcome. Finally, an understanding of the vaccine correlates of protection and correlates of durability of protection in persons with and without previous COVID-19 infection would assist policy makers in creating sound programmatic decisions.

SAGE as well as the Technical Advisory Group on COVID-19 Vaccine Composition continue to monitor the situation carefully and the WHO position will be updated accordingly.

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